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EXAMINER	
GOON, SCARLETT Y	
ART UNIT	PAPER NUMBER
1623	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,110	XU ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 6-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 9-12* is/are rejected.

7)☒ Claim(s) *6-8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 15 September 2008 in which claims 2-5 and 13-20 were cancelled, and claims 1 and 6-12 are amended to change the scope and breadth of the claims.

Support for the amendments to claims 1 and 6-12 can be found in Examples 1-10 of Applicant's specification.

Claims 1 and 6-12 are currently pending and are examined on the merits herein.

Priority

This application is a National Stage entry of PCT/CN03/00609 filed on 29 July 2003 and claims priority to China foreign application 02125917.8 filed on 2 August 2002. A certified copy of the foreign priority document in Chinese has been received. No English translation has been received.

Objections Withdrawn

In view of the cancellation of claims 15 and 16, all objections made with respect to claims 15 and 16 in the previous Office Action are withdrawn.

Applicant's amendment, filed 15 September 2008, with respect to the objections of claims 6, 7 and 10 has been fully considered and is persuasive because the amendment corrects the identified informalities.

These objections have been **withdrawn**.

Rejections Withdrawn

In view of the cancellation of claims 13-20, all rejections made with respect to claims 13-20 in the previous Office Action are withdrawn.

These rejections have been **withdrawn**.

The following are new ground(s) or modified rejections necessitated by Applicants' amendment, filed on 15 September 2008, wherein the limitations in pending claims 1 and 12 as amended now have been changed; claims 6-8 depend from claim 1, and claims 9-11 depend from claim 12. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, dated 14 May 2008, have been modified and are listed below.

Claim Objections

Claim 1 is objected to because of the following informalities: Monoester is incorrectly spelled. Appropriate correction is required.

Claims 9-11 are objected to because of the following informalities:

A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

A claim which depends from a dependent claim should not be separated by any claim which does not also depend from said dependent claim. It should be kept in mind

that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of a "derivative" in claim 1 renders the claim herein indefinite. The recitation of "riboflavin derivatives" is not clearly defined in the specification. The 10th edition of the Merriam-Webster's Collegiate Dictionary (Merriam-Webster Incorporated: Springfield, Massachusetts, 1993, pp 311) defines "derivative" as, "a chemical substance related structurally to another substance and theoretically derivable from it." Thus, it is unclear whether the recitation "riboflavin derivatives" refer to the compounds in the indicated select group or whether the riboflavin derivatives can include modifications to the compounds in the indicated select group. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to "riboflavin derivative" herein. Thus, it is unclear and indefinite as to how the "derivative" herein is encompassed thereby.

The recitation “isobutyrate of riboflavin,” “riboflavin-2,6-dimethoxybenzoate,” and “adamantane acid ester of riboflavin” renders the claim herein indefinite. As riboflavin contains four possible hydroxyl groups, at the 2’, 3’, 4’, and 5’ positions of the chain, it is unclear whether the ester modification occurred at one or more select hydroxyl position(s) or on all of the hydroxyl groups.

Claim 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to carry out the method of using the compound to treat the said diseases. Furthermore, it is respectfully suggested that Applicants amend the claim language to read “method of treating” rather than “method of using” if Applicants intend to use the compound in a method to treat a condition.

Response to Arguments

Applicant's arguments filed 15 September 2008 with respect to the rejection of claim 1 made under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and instantly claim the subject matter which applicant regards as the invention, have been fully considered but they are not persuasive.

Applicants argue that the amendment to the claim to include riboflavin derivatives selected from the group as indicated in the claim now renders the claim definite. However, as indicated above, it is unclear whether the recitation "riboflavin derivative” only includes the compounds as claimed or whether it can encompass modifications to

the recited compounds. New grounds of rejection for the currently amended claims, necessitated by Applicant's amendments, are as indicated above.

The rejection is still deemed proper and therefore adhered to.

Applicant's arguments filed 15 September 2008 with respect to the rejection of claims 9-20 made under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and instantly claim the subject matter which applicant regards as the invention, have been fully considered but they are not persuasive.

Applicants argue that the amendment to the claim to include the language "method of" more definitely defines what the Applicants intend to claim and further indicates that the claim has been amended to require method steps. However, as indicated above, the claimed method still lacks steps for carrying out the method. The recitation of a method without any steps renders the claims herein indefinite as it does not teach one how to carry out the method. New grounds of rejection for the currently amended claims, necessitated by Applicant's amendments, are as indicated above.

The rejection is still deemed proper and therefore adhered to.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of treating ariboflavinosis, digestive tract catarrh, and persistent oral ulcer using the compound of formula (II) does not reasonably provide enablement for the method of treating any disease with all/any of the compounds of claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected invention is drawn to a method of using the compounds of claim 1 to treat a disease.

Breadth of claims: The claims are extremely broad in that they encompass literally all known diseases. The claims further encompass treatment using any of the compounds of claim 1.

Amount of guidance/Existence of working examples: Working examples are present which only show that the compound of formula (II) are effective for the treatment of ariboflavinosis, digestive tract catarrh, and persistent oral ulcer. There is no guidance in the specification, nor are there any working examples, to show that any other riboflavin esters, such as the isobutyrate of riboflavin, riboflavin-2,6-dimethoxybenzoate, and admantane acid ester of riboflavin, are effective for treating ariboflavinosis, digestive tract catarrh, or persistent oral ulcer. Additionally, there is no guidance in the specification that the compounds of claim 1 can treat any disease, as indicated in instant claim 12.

Lack of a working example is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

State of the prior art/Predictability or unpredictability of the art: The prior art teaches that riboflavin is used therapeutically to ameliorate ariboflavinosis (PTO-892, ref. A), and that riboflavin in combination with amino acids and effectors of the urea cycle are effective in alleviating or reducing the effects of fatigue and weakness associated with cancer and cytotoxic cancer chemotherapy (PTO-892, ref. B). Additionally, the prior art teaches that riboflavin-5'-monobutyrate and riboflavin tetrabutyrate have the same nutritional activity as riboflavin, suggesting that the ester compounds are easily hydrolyzed to riboflavin, and therefore can be used to treat ariboflavinosis. On the other hand, the prior art also teaches that riboflavin-5'-monopalmitate has very little riboflavin activity while riboflavin tetrapalmitate does not have any riboflavin activity because these ester compounds are slow to hydrolyze to

riboflavin (PTO-892, Ref. U). This suggests that only small ester modifications of riboflavin are efficiently converted to the natural riboflavin compound and larger ester modifications of riboflavin are not converted to riboflavin very efficiently. Thus, one of ordinary skill in the art would view modifications to riboflavin that include an adamantane or benzoate structure to be large ester modifications, and therefore unlikely to be used in the treatment of ariboflavinosis and other diseases that require riboflavin.

Furthermore, as diseases are known to arise from different disorders, syndromes, infections, injuries, etc., a skilled artisan would view it highly unlikely that the compounds of claim 1 can be used to treat all and any disease.

Therefore, in view of the *Wands* factors as discussed above, there is no clear and convincing evidence in sufficient support of the use of all the claimed riboflavin derivatives of claim 1 to treat any disease, including ariboflavinosis, digestive tract catarrh, and persistent oral ulcer.

Response to Arguments

Applicant's arguments filed 15 September 2008 with respect to the rejection of claims 9-20 made under 35 USC § 112, first paragraph, for lack of enablement, have been fully considered but they are not persuasive.

Applicants argue that the amendment to the claims by canceling those claims encompassing diseases other than ariboflavinosis, digestive tract catarrh, and persistent oral ulcer and amending the existing claim 1 to include only the indicated

riboflavin compounds overcomes the lack of enablement rejection. This argument is not persuasive because the amended claims changes the scope of the claims, as indicated in the rejection of claims 9-12 above. New grounds of rejection for the currently amended claims, necessitated by Applicant's amendments, are as indicated above.

The rejection is still deemed proper and therefore adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Section [0001]

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards *et al.* (PTO-892, Ref V).

Edwards *et al.* disclose the photochemical and pharmacokinetic properties of selected flavin compounds. The compounds include riboflavin, lumiflavin and the 2', 3', 4', 5'-tetraacetyl, -tetrapropionyl, -tetrabutyrl and -tetrapalmitoyl esters of riboflavin (abstract). These compounds are shown in figure 1 (p. 37). The tetrapropionyl ester of riboflavin disclosed by Edwards *et al.* differs from the instantly claimed compound, isobutyrl ester of riboflavin by the substitution of a methyl group in place of a hydrogen on the alkyl chain.

One skilled in the art would have found the claimed compound *prima facie* obvious because it is well established that the substitution of a methyl group for a hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re Lincoln*, 126 USPQ 477, 53 USPQ 40 (CCPA 1942); *In re Druey*, 319 F.2d 237, 138 USPQ 39 (CCPA 1963); *In re Lohr*, 317 F.2d 388, 137 USPQ 548 (CCPA 1963); *In re Hoehsema*, 399 F.2d 269, 158 USPQ 598 (CCPA 1968); *In re Wood*, 582 F.2d 638, 199 USPQ 137 (CCPA 1978). The motivation to make the claimed compound derives from the expectation that structurally similar compounds possess similar activity (i.e. pharmacological use).

Thus, the instantly claimed isobutyrate ester of riboflavin is *prima facie* obvious over the teachings of Edwards *et al.*

Response to Arguments

Applicant's arguments filed 15 September 2008 with respect to the rejection of claims 1 and 2 made under 35 USC § 102(b) as being unpatentable over Edwards *et al.*, have been fully considered but they are not persuasive.

Applicants argue that the Edwards *et al.* reference does not teach the compounds as described in the currently amended claims. This argument is not persuasive because the references were applied to the claims in the preliminary amendment filed on 14 May 2005, not to the currently amended claims.

The rejection is still deemed proper and therefore adhered to.

Section [0002]

Claims 9, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over research publication by Edwards *et al*. (PTO-892, Ref. V) as applied to claim 1 above, and further in view of Okuda *et al.* (PTO-892, Ref. U) and US Patent No. 6,565,891 to Chandra (herein referred to as the '891 patent, PTO-892, Ref. A).

The teachings of Edwards *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103. Edwards *et al.* does not teach a method of treating ariboflavinosis or persistent oral ulcer using a compound of claim 1.

Okuda *et al.* teach nutritional and ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate. To test the nutritional effects of the riboflavin derivatives, rats were fed either a standard diet, a riboflavin-deficient diet, a riboflavin-deficient diet supplemented with riboflavin-5'-monobutyrate suspended in olive oil, or a riboflavin-deficient diet supplemented with riboflavin-5'-monopalmitate suspended in olive oil (p. 9, under subheading "methods"). The authors previously showed that riboflavin tetrabutyrate had the same vitamin B_2 activity (nutritional and ariboflavinosis-curing effects) in young rats as riboflavin, but riboflavin tetrapalmitate did not have vitamin B_2 activity as rats administered riboflavin tetrapalmitate clearly showed ariboflavinosis. Similar to riboflavin tetrabutyrate, rats fed a diet supplemented with riboflavin-5'-monobutyrate exhibited vitamin B_2 activity (p. 13, second full paragraph). However, rats fed a diet supplemented with riboflavin-5'-monopalmitate showed signs of lower vitamin B_2 activity. Their results suggest that riboflavin-5'-monobutyrate is easily hydrolyzed to riboflavin, and hence has the same nutritional effect as riboflavin, while

riboflavin-5'-monopalmitate was only slowly hydrolyzed to riboflavin (p. 13, last paragraph).

The '891 patent teaches a nutritional supplement for children that is most effective in optimizing health, increasing the immunity, and decreasing the instances and severity of infection, particularly among children (abstract). The importance of each of the component vitamins and minerals making up the nutritional supplement is described in detail. Of particular relevance, is the importance of riboflavin in the nutritional supplement. The '891 patent teaches that riboflavin participates in oxidation-reduction reactions in numerous metabolic pathways and in energy production via the respiratory chain (column 7, lines 22-31). It is used therapeutically to ameliorate ariboflavinosis resulting from diverse causes such as inadequate dietary intake, decreased assimilation, rare genetic defects in the formation of specific flavoproteins, hormonal disorders and after use of certain drugs. Symptoms indicating riboflavin deficiency include rough skin, angular stomatitis, cracked lips, and mouth ulcers.

It is noted that the Okuda *et al.* reference does not teach the tetrapropionyl ester of riboflavin as disclosed by Edwards *et al*. However, as the tetrapropionyl ester of riboflavin has close structural similarity to the tetrabutyryl ester of riboflavin (differing in only one methylene unit) which is taught by Edwards *et al.*, and as discussed above, is structurally similar to the instantly claimed isobutyrate ester of riboflavin, one of ordinary skill in the art would expect the compounds to have similar results. Thus, as suggested by Edwards *et al.*, short chain esters of riboflavin exhibit similar biochemical properties to other short chain esters of riboflavin (such as acetyl and propionyl esters) and

therefore would be expected to hydrolyze to riboflavin, as discussed by Okuda *et al.* Also, see below for recitation of section from MPEP § 2144.09 regarding structural homologs.

The following is a quotation of MPEP § 2144.09:

> **Compounds which are** position isomers (compounds having the same radicals in physically different positions on the same nucleus) or **homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity** that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Edwards *et al.*, concerning various esters of riboflavin compounds, with the teachings of Okuda *et al.*, regarding the nutritional and ariboflavinosis-curing effects of riboflavin tetrabutyrate and riboflavin-5'-monobutyrate, with the teachings of the '891 patent, regarding the various symptoms of riboflavin deficiency. Since the instantly claimed isobutyrate ester of riboflavin is structurally similar to the tetrapropionyl ester of riboflavin taught by Edwards *et al.* which is structurally similar to the tetrabutyryl ester of riboflavin taught by both Edwards *et al.* and Okuda *et al.*, one of ordinary skill in the art would expect that the isobutyrate ester of riboflavin and tetrapropionyl ester of riboflavin would behave similarly to the tetrabutyryl ester of riboflavin with respect to its ease in hydrolysis to riboflavin, and thus have similar ariboflavinsos curing effect and treatment of persistent oral ulcers.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 15 September 2008 with respect to the rejection of claims 9, 11, 13 and 17 made under 35 USC § 103(c) as being unpatentable over Edwards *et al.*, further in view of Okuda *et al.* and US Patent No. 6,565,891 to Chandra, have been fully considered but they are not persuasive.

Applicants argue that since the Edwards *et al.* reference does not teach the compounds as described in the currently amended claims, the combination of the Okuda *et al.* and Chandra references with Edwards *et al.* does not cure the deficiency of Edwards *et al.* in replicating the presently claimed invention. This argument is not persuasive because the references were applied to the claims in the preliminary amendment filed on 14 May 2005, not to the currently amended claims.

The rejection is still deemed proper and therefore adhered to.

Section [0003]

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over research publication by Edwards *et al*. (PTO-892, Ref. V) as applied to claim 1 above, and further in view of Okuda *et al.* (PTO-892, Ref. U) and PG Pub No. US 2003/0105104 A1 by Burzynski (PTO-892, Ref. B).

The teachings of Edwards *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103. Edwards *et al.* further teach that the increase in hydrophobicity of the ester compounds of riboflavin enhance its affinity for tumors and other kinds of proliferating cells (p. 37, column 1).

Edwards *et al.* does not teach a method of treating digestive tract catarrh caused by bone marrow transplantation, leukemia or chemotherapy using a compound of claim 1.

The teachings of Okuda *et al.* were as described above in section [0002] of the claim rejections under 35 USC § 103.

Burzynski teaches a pharmaceutical composition comprising riboflavin, effectors of the urea cycle, and amino acids, suitably combined with appropriate carriers, diluents, or excipients (abstract; paragraph 0001 and 0008; claim 14), as well as a method for alleviating or reducing the toxic, nutritional and metabolic disturbances associated with cancer and cancer chemotherapy by administering the said composition to a cancer patient in need thereof (paragraph 0024; claim 1). Common side effects associated with cancer treatment include tiredness, loss of appetite, mucositis, diarrhea and myelosuppression (paragraph 0072). In example 1 (paragraphs 0070-0073), Burzynski shows that when a female patient diagnosed with adenocarcinoma of the colon was administered a composition comprising a sterile solution of six amino acids, L-arginine, and riboflavin prior to treatment by chemotherapy with 5-fluorouracil, the patient did not experience the side effects typically associated with the chemotherapy treatment.

It is noted that Burzynski does not explicitly teach that digestive tract catarrh is a side effect of cancer chemotherapy. However, as evidenced by McCarthy *et al.* (PTO-892, Ref. W), oral mucositis is an inflammation and ulceration of the oral mucosa and myelosuppression (abstract; p. 484, column 2) from chemotherapy of the digestive tract.

It is further noted that Burzynski does not specifically teach the administration of ester analogs of riboflavin to cancer patients exhibiting the common side effects of chemotherapy. However, as described above in section [0002] of the claim rejections under 35 USC § 103, Okuda *et al.* teach that esters of riboflavin can be hydrolyzed to the natural riboflavin compound and thus exhibit activity similar to riboflavin. Therefore, esters of riboflavin can serve as functional substitutes for natural riboflavin when administered in a composition.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Edwards *et al.*, concerning various esters of riboflavin compounds, with the teachings of Okuda *et al.*, regarding the nutritional and ariboflavinosis-curing effects of riboflavin tetrabutyrate and riboflavin-5'-monobutyrate, with the teachings Burzynski, regarding a pharmaceutical composition comprising riboflavin, effectors of the urea cycle and amino acids in the treatment of side effects, such as mucositis, resulting from cancer chemotherapy. Since the instantly claimed isobutyrate ester of riboflavin is structurally similar to the tetrapropionyl ester of riboflavin taught by Edwards *et al.* which is structurally similar to the tetrabutyryl ester of riboflavin taught by both Edwards *et al.* and Okuda *et al.*, and Okuda *et al.* further teach that esters of riboflavin can be hydrolyzed to the natural riboflavin compound and thus exhibit activity similar to riboflavin, one would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Edwards *et al.*, that the increase in hydrophobicity of the ester compounds of riboflavin enhance its affinity for tumors and other kinds of proliferating cells (p. 37, column 1).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments filed 15 September 2008 with respect to the rejection of claims 10 and 15 made under 35 USC § 103(c) as being unpatentable over Edwards *et al.*, further in view of Okuda *et al.*, PG Pub US No. 2003/0105104 A1 to Burzynski, and McCarthy *et al.*, have been fully considered but they are not persuasive.

Applicants argue that since the Edwards *et al.* reference does not teach the compounds as described in the currently amended claims, the combination of the Okuda *et al.*, Burzynski and McCarthy *et al.* references with Edwards *et al.* does not cure the deficiency of Edwards *et al.* in replicating the presently claimed invention. This argument is not persuasive because the references were applied to the claims in the preliminary amendment filed on 14 May 2005, not to the currently amended claims.

The rejection is still deemed proper and therefore adhered to.

Applicant's arguments filed 15 September 2008 with respect to the rejection of claims 12 and 19 made under 35 USC § 103(c) as being unpatentable over Edwards *et al.*, further in view of Nagatomo *et al.*, have been fully considered but they are not persuasive.

Applicants argue that since the Edwards *et al.* reference does not teach the compounds as described in the currently amended claims, the combination of the

Okuda *et al.* and Nagatomo *et al.* references with Edwards *et al.* does not cure the deficiency of Edwards *et al.* in replicating the presently claimed invention. This argument is not persuasive because the references were applied to the claims in the preliminary amendment filed on 14 May 2005, not to the currently amended claims.

The rejection is still deemed proper and therefore adhered to.

Allowable Subject Matter

Claims 6-8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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